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Free-living energy expenditure reduced after deep brain stimulation surgery for Parkinson's disease

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Key words

chronic bilateral subthalamic stimulation; doubly labelled water; energy metabolism; substrate oxidation rate; weight gain

Summary

Background: The clinical picture in Parkinson's disease (PD) is characterized by bradykinesia, rigidity, resting tremor and postural instability. In advanced stages of the disease, many patients will experience reduced efficacy of medication with fluctuations in symptoms and dyskinesias. Surgical treatment with deep brain stimulation in the subthalamic nucleus (STN-DBS) is now considered the gold standard in fluctuating PD. Many patients experience a gain of weight following the surgery. The aim of this study was to identify possible mechanisms, which may contribute to body weight gain in patients with PD following bilateral STN-DBS surgery.

Methods: Ten patients with PD were studied before bilateral STN-DBS surgery, and seven patients were studied again 3 and 12 months postoperatively. Clinical examination and resting metabolic rate with and without medical treatment was measured before and after STN-DBS. Furthermore, free-living energy expenditure, body composition, energy intake, peak oxygen consumption, maximal workload and leisure time physical activity were measured before and 3 and 12 months after surgery.

Results: The STN-DBS operated patients had a significant weight gain of 4·7 ± 1·6 kg (mean ± SE) 12 months postoperatively, and the weight gain was in the fat mass. The free-living energy expenditure decreased postoperatively 13 ± 4% even though the reported dietary intake was reduced. A decreased energy expenditure took place in the non-resting energy expenditure. The reported daily leisure time activity, peak oxygen consumption and maximal workload were unchanged.

Conclusion: The STN-DBS operated patients have a significant postoperative weight gain, as a result of a decrease in free-living energy expenditure concomitant with an insufficient decrease in energy intake.

Introduction

Parkinson's disease (PD) is a progressive neurologic disorder, which mainly affects the nigrostriatal system. The four cardinal signs in PD are bradykinesia, rigidity, resting tremor and postural instability. Dopaminergic therapies such as levodopa or dopamine agonists usually improve symptoms and signs very effectively in the first 5–7 years. However, the progression of disease is inevitable, and after years in medical treatment, many patients will experience reduced efficacy of medication.

The introduction of deep brain stimulation (DBS) of the subthalamic nucleus (STN) in the treatment of advanced, fluctuating parkinsonism has altered the treatment of late-stage PD dramatically and is now considered the most effective surgical procedure for patients with PD and intractable fluctuations (Krack *et al.*, 2003). The treatment leads to a great reduction in on-off phenomena and a large improvement of L-dopa-induced dyskinesias as the anti-parkinsonian medication can be reduced considerably. Many patients experience a large gain of weight in the period following the implantation of DBS devices, where most of the studies on weight gain have focused on bilateral STN stimulation (Barichella *et al.*, 2003; Macia *et al.*, 2004; Perlemoine *et al.*, 2005; Tuite *et al.*, 2005; Montaurier *et al.*, 2007; Walker *et al.*, 2009b; Strowd *et al.*, 2010; Locke

et al., 2011) However, weight gain has also been described after unilateral STN stimulation and globus pallidus internus DBS (Walker *et al.*, 2009a; Locke *et al.*, 2011).Some of these patients had a low weight beforehand, so their gain has normalized the weight; others develop overweight (Barichella *et al.*, 2003; Macia *et al.*, 2004). In patients with documented weight gain postoperatively, the gain has been correlated with reduction in hyperkinesias (Romito *et al.*, 2002). Subsidence of chronic tremor could cause decreased energy expenditure (Tuite *et al.*, 2005). Macia *et al.* (2004) found a postoperative decrease in energy expenditure, especially for patients with many fluctuations and dyskinesias preoperatively, and the postoperative weight gain was correlated with reduction in L-dopa doses. However, a stimulatory effect on the metabolic rate of DBS cannot be excluded.

The aim of this study was to identify possible mechanisms that may contribute to body weight gain in patients with PD following bilateral STN-DBS. We therefore measured body composition, free-living energy expenditure, energy intake and resting metabolic rate in a group of patients pre- and postoperatively. Furthermore, the resting metabolic rate was measured with and without medical treatment and DBS.

Material and methods

Subjects

The study enrolled 10 patients with PD (seven men) who were operated with bilateral STN-DBS. Mean (SD) history of disease was 13·3 (4·8) years, and they all suffered from severe motor fluctuations that were not improved by changes in their anti-parkinsonian medication. Mean (SD) age was 61·7 (6·5) years. The patients were approved for surgery according to following selection criteria (Defer *et al.*, 1999): disease duration >5 years, age under 70 years, excellent response to apo-morphine or levodopa challenge, no surgical contraindications, and no dementia or major ongoing psychiatric illness. Of these patients, one got a cerebral haemorrhagia during surgery and one patient did not wish to continue follow-up after surgery. One patient died 10 months after the STN-DBS surgery (complication to pneumonia). Seven patients completed the whole study, which included a pretest and a 3- and 12-month follow-up after surgery. The subjects were given a written and oral description of the study before giving their voluntary consent to participate. The Scientific Ethical Committees of The Capital Region approved the study (project nr KF(01)259416).

Study design

Patients were studied before and again 3 and 12 months after STN-DBS surgery.

The following same measurements were taken over a 4-day period: On day 1, a clinical examination and an interview on health and medical history were performed. Body composition, peak oxygen consumption and leisure time physical activity were measured. In the morning on day 2–4, resting energy expenditure (REE) was measured. In the following 14 days, the free-living energy expenditure was measured.

Unified Parkinson's Disease Rating Scale

Following the test, evaluation of signs of PD was performed using the motor component of the Unified Parkinson's Disease Rating Scale (UPDRS), which includes assessment of general bradykinesia, rigidity (neck, arms, legs) and tremor (face, hands, feet, action tremor) (Ramaker *et al.*, 2002; Goetz *et al.*, 2008). UPDRS III was performed before surgery in best ON with medication and without medication after withdrawal overnight (OFF). After surgery, UPDRS III was performed at three and 12 months, on three consecutive days: without medication and without STN-DBS stimulation ('off' stimulation, 'off' medication), with STN-DBS stimulation but without anti-parkinsonian medication ('on' stimulation, 'off' medication) and with STN-DBS stimulation and with anti-parkinsonian medication ('on' stimulation, 'on' medication).

Stage of disease (Hoehn and Yahr) was assessed (Goetz *et al.*, 2004).

Body composition

Patient's fat mass and fat-free mass (FFM) were determined by DEXA-scanning (Lunar DPX-IQ, software version 4.6c; Lunar Corporation, Madison, WI, USA).

Resting energy expenditure

In the evening before measurement, the anti-parkinsonian medication was paused at 20:00, and the next morning (day 2) REE was determined by indirect calorimetry in the resting and fasting (12 h) condition (defined 'off' medication). On day 3 in the morning, REE was determined again, but where the patients were on their normal anti-parkinsonian medication ('on' medication). Oxygen consumption and carbon dioxide output were measured continuously with an Oxycon Champion System using facemask and the breath-by-breath technique for a period of 30–45 min. Values for REE and substrate oxidation rates were calculated from the oxygen consumption and the respiratory exchange ratio (RER) (Ferrannini, 1988). Protein oxidation was assumed to be 60 g day^{-1}, corresponding to about 15% of basal metabolic rate (Perlemoine *et al.*, 2005).

The measurements of REE performed 3 and 12 months after STN-DBS surgery were as follows: on day 2 without medication and without STN-DBS stimulation ('off' stimulation, 'off' medication), on day 3 with STN-DBS stimulation but without anti-parkinsonian medication ('on' stimulation, 'off' medication) and on day 4 with STN-DBS stimulation and with anti-parkinsonian medication ('on' stimulation, 'on' medication).

Non-resting energy expenditure

Non-resting energy expenditure was calculated as the total energy expenditure during free living minus REE during 'on' medication and postoperatively 'on' medication and 'on' stimulation.

Total daily energy expenditure

Free-living daily energy expenditure (DEE) was determined over a 14-day period using the doubly labelled water technique while the patients consumed their usual prescribed medication and after surgery with STN-DBS stimulation. Baseline urine samples were obtained for background measurements, and an oral dose of $^{2}H_2O$ (0·125 g kg^{-1} estimated body water) and $H_2{}^{18}O$ (0·25 g kg^{-1} estimated body water) was administered in the evening of day 2. Two urine samples were obtained the following morning and 7 and 14 days later (morning urine) (Westerterp *et al.*, 1995). The urine samples were stored at −20°C until analysis took place. The isotopes deuterium (^{2}H) and oxygen-18 (^{18}O) in the urine were analysed by isotope ratio mass spectrometry (Optima; VG Isogas Ltd, Middlewich, Cheshire, UK). The carbon dioxide (CO_2) production rate was calculated from the elimination rates of the two stable isotopes using the equation of Schoeller (1988). The respiratory quotient (RQ) was taken to be equal to the food quotient of the diet and was taken as 0·85 (Black *et al.*, 1986). The energy expenditure was calculated based on the carbon dioxide production rate and RQ.

Peak oxygen consumption

Peak oxygen consumption was determined by indirect calorimetry (Oxycon Champion; Jaeger, Wuerzburg, Germany). The subjects exercised on an electrically braced cycle ergometer (ergometrics er900; ergoline, Bitz, Germany). The initial workload was 30 W and was increased by 30 W every 2 min until exhaustion. Oxygen uptake and carbon dioxide output were measured using facemask and the breath-by-breath technique.

Energy intake

Energy intake was determined from a 3-day food diary. Patients were provided with a dietary scale and instructed on the measurement of food intake. The patients were strongly encouraged not to change their dietary habits during the measurement period. The calculation was performed in http://www.madlog.dk. The energy intake was measured during the doubly labelled water measurement period.

Leisure time physical activity

The level of physical activity spent by the patients over a 7-day period was scored using a questionnaire for elderly. The questionnaire scores the activity level with regard to leisure time, household and work-related activity. Scores were calculated according to the PASE Administration and Scoring Instruction manual (Washburn *et al.*, 1993).

Statistical analysis

All data from experiments are given as mean ± SEM. The data were analysed by a paired *t*-test for each time point. $P<0·05$ was considered significant.

Results

The staging scale as measured by the Hoehn and Yahr was 2·3 ± 0·1 at enrolment and did not change during the study.

Preoperative

Physical characteristics of the 10 enrolled patients are shown in Table 1. Furthermore, the parkinsonian symptoms and REE with and without anti-parkinsonian medication are shown. There was a significantly increased resting oxygen uptake with the patients 'off' drug compared with 'on' drug, and a non-significant increased REE 'off' drug compared with 'on' drug ($P = 0·065$), while RER was unchanged.

Seven patients fulfilled the whole follow-up period, and the following postoperative results are from these seven patients.

Parkinsonian symptoms

There was, as expected, a significant improvement in UPDRS III and IV after surgery (data not shown). Anti-parkinsonian medication was reduced postoperatively; however, it did not

Table 1 Physical characteristics, parkinsonian symptoms and resting energy expenditure in the 10 preoperative patients 'on' and 'off' their anti-parkinsonian medication.

N = 10	Preoperative
Height (cm)	174·0 ± 2·3
Body weight (kg)	78·1 ± 3·1
BMI (kg m^{-2})	25·8 ± 0·7
Fat mass (kg)	20·7 ± 1·7
Fat mass (%)	27·7 ± 2·3
Fat-free mass (kg)	57·4 ± 3·1
UPDRS III on drug	19·6 ± 3·1
UPDRS III off drug	41·4 ± 3·4*
UPDRS IV on drug	7·3 ± 0·6
L-dopa equivalent dose (mg day^{-1})	878 ± 118
Resting oxygen uptake (ml min^{-1}) on drug	272 ± 12
Resting oxygen uptake (ml min^{-1}) off drug	304 ± 12*
Respiratory exchange ratio on drug	0·74 ± 0·01
Respiratory exchange ratio off drug	0·72 ± 0·01
Resting energy expenditure on drug (MJ day^{-1})	7·7 ± 0·4
Resting energy expenditure off drug (MJ day^{-1})	8·6 ± 0·4

Mean ± SEM. *$P<0·05$ (pared *t*-test) compared with measurement on anti-parkinsonian medication.

Table 2 Body composition and anti-parkinsonian medication before and after deep brain stimulation in the subthalamic nucleus surgery.

N = 7	Preoperative	3 months after	12 months after
L-dopa equivalent dose (mg day^{-1})	873 ± 108	551 ± 99	598 ± 91
Body weight (kg)	79·4 ± 4·4	82·7 ± 3·9	84·1 ± 3·7*
BMI (kg m^{-2})	25·5 ± 0·9	26·5 ± 0·8	27·0 ± 0·8*
Fat mass (kg)	19·6 ± 1·9	22·6 ± 2·3*	23·5 ± 2·5*
Fat mass (%)	25·7 ± 2·1	28·4 ± 2·7*	29·0 ± 2·9
Fat-free mass (kg)	59·8 ± 3·7	60·1 ± 3·6	60·6 ± 3·2

Mean ± SEM. *P<0·05 (pared t-test) compared with preoperative values.

reach significance (P = 0·064 after 3 months and P = 0·072 after 12 months) (Table 2).

Body composition

There was a significant increase in body weight at 4·7 kg (range 2·0–11·5 kg) 12 months after the operation, and the increase took place in the fat mass whereas the FFM was unchanged (Table 2).

Resting energy expenditure

During anti-parkinsonian medication was the preoperative resting oxygen consumption (VO_2) 283 ± 13 ml min^{-1}, the REE 8·00 ± 0·3 MJ day^{-1} and the RER 0·75 ± 0·2, and these parameters did not change significantly 'on' drug/'on' stimulation 3 and 12 months postoperatively. In Fig. 1 is shown the VO_2, REE and RER 3 and 12 months after surgery.

Three and 12 months after operation, there were no significant differences in VO_2 and REE comparing values 'on' drug/'on' stimulation with values 'off' drug/'off' stimulation and 'off' drug/'on' stimulation (Fig. 1). However, during STN-DBS stimulation, the RER was significantly increased compared with off drug/'off' stimulation three and 12 months after surgery (Fig. 1).

Substrate oxidation rates

The substrate oxidation rates after surgery is shown in Fig. 2. Preoperatively, there was no significant difference in fasting carbohydrate oxidation or lipid oxidation during anti-parkinsonian medication ('on' drug) compared with 'off' drug (data not shown). After the operation, the resting fasting lipid oxidation decreased significantly when the patients were 'on' stimulation compared with 'off' drug/'off' stimulation at both 3 and 12 months visit (Fig. 2).

Daily energy expenditure

The DEE is shown in Table 3. The free-living DEE decreased, although not significantly 3 months after surgery (P = 0·053)

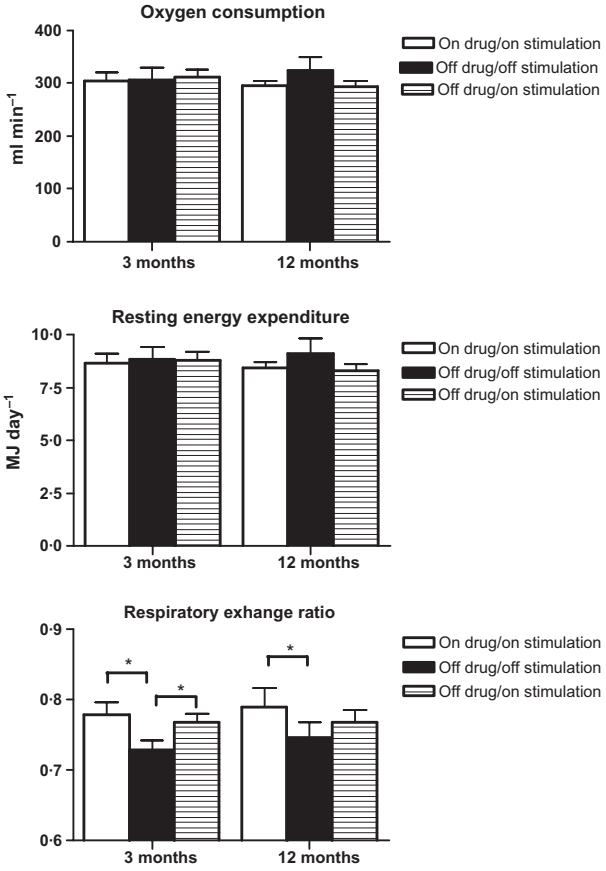

Figure 1 Whole-body fasting oxygen consumption, resting energy expenditure and respiratory exchange ratio 3 and 12 months after the deep brain stimulation in the subthalamic nucleus (STN-DBS) surgery: Open bars are with the patients on DBS and on their anti-parkinsonian medication. Closed bars are with the patients without DBS and without their anti-parkinsonian medication for 12 h. Hatched bars are with the patients without their anti-parkinsonian medication for 12 h but during DBS.

and was significantly decreased with 13 ± 4% 12 months after the operation compared with the preoperative value (Table 3).

Non-resting energy expenditure

The non-resting energy expenditure is the amount of the DEE not coming from REE when the patients are 'on' medication and postoperatively 'on' medication and 'on' stimulation. It was significantly decreased by 42 ± 9% 3 months after surgery and by 41 ± 8% 12 months after surgery compared with the preoperative value (Table 3).

Daily energy intake

The reported daily energy intake (DEI) decreased significantly 12 months after the operation compared with preoperative values (Table 3). The reported DEI accounted for about 70% of the DEE.

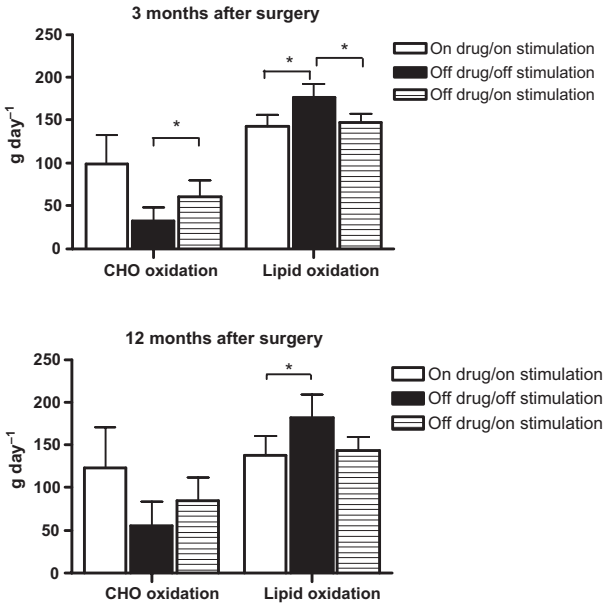

Figure 2 Whole-body fasting substrate oxidation rates 3 and 12 months after the deep brain stimulation in the subthalamic nucleus (STN-DBS) surgery: Open bars are with the patients on DBS and on their anti-parkinsonian medication. Closed bars are with the patients without DBS and without their anti-parkinsonian medication for 12 h. Hatched bars are with the patients without their anti-parkinsonian medication for 12 h but during DBS.

Table 3 Daily free-living energy expenditure (DEE), non-resting energy expenditure (non-REE), reported daily energy intake (DEI), peak oxygen uptake, maximal workload and reported physical activity (PASE) before and after deep brain stimulation in the subthalamic nucleus surgery.

N = 7	Preoperative	3 months after	12 months after
DEE (MJ day^{-1})	13·3 ± 1·1	11·4 ± 0·6	11·3 ± 0·6*
Non-REE (MJ day^{-1})	5·2 ± 0·9	2·7 ± 0·4*	2·9 ± 0·5*
DEI (MJ day^{-1})	10·1 ± 1·0	8·6 ± 1·1	8·0 ± 0·6*
Peak VO_2 (l min^{-1})	2·4 ± 0·4	2·4 ± 0·4	2·4 ± 0·2
Peak VO_2 (ml kg^{-1} min^{-1})	30 ± 4	28 ± 3	28 ± 2
Maximal workload (W)	138 ± 27	146 ± 22	139 ± 15
PASE	174 ± 25	148 ± 12	159 ± 26

Mean ± SEM. *P<0·05 (pared t-test) compared with preoperative values.

Peak oxygen uptake and maximal workload

The peak oxygen uptake and maximal workload is shown in Table 3. There was no difference in peak oxygen uptake or maximal workload during the study period.

Leisure time physical activity

The physical activity score did not change significantly 3 or 12 months after surgery (Table 3).

Discussion

This study is the first long-term prospective study, where free-living energy expenditure has been extensively evaluated before and 3 and 12 months after STN-DBS surgery. All patients experienced a much better motor performance similar to previously reported studies with effect on levodopa-responsive perkinsonian features such as bradykinesia, tremor and rigidity with a reduction in the need for anti-parkinsonian medication (Limousin *et al.*, 1998; Moro *et al.*, 1999).

The main finding is that the STN-DBS operated patients had a significant weight gain postoperatively and that the weight gain was taking place in the fat mass. This is in agreement with a recent study (Bannier *et al.*, 2009), where patients were examined before and 3 and 16 months after STN-DBS operation. The increase in weight was attributed to a decrease in total energy expenditure concomitant with an insufficient decrease in energy intake. Furthermore, the decrease in total energy expenditure was taking place in the non- REE.

During weight stable conditions, the energy intake is equal to the energy used (total energy expenditure). If an individual is in positive energy balance, there will be a weight gain because of storing of energy.

The decrease in total energy expenditure after surgery in the present study was about 2 MJ day^{-1}, which theoretically would led to a weight gain at about 20 kg after 1 year assuming unchanged daily caloric intake postoperatively, and all the extra energy deposited as fat.

Only very few earlier studies have measured free-living energy expenditure in patients with PD using the doubly labelled water technique (Toth *et al.*, 1997; Delikanaki-Skaribas *et al.*, 2009). The mean DEE in these studies was about 25% lower than in the present study. However, in these studies they investigated patients on levodopa medication without severe dyskinesias. Therefore, this discrepancy can be explained by difference in weight, age and severe dyskinesias as our patients were candidates for operation.

An earlier study (Montaurier *et al.*, 2007) has measured the effect of STN-DBS on the DEE evaluated in a calorimetric chamber before and 3 months after surgery. They found a significant reduction by about 9%, and although this result was under controlled conditions, it is in accordance with the present results. Furthermore, they found unchanged REE 3 months postoperatively in accordance with the results in the present study, where the REE with the patients on anti-parkinsonian medication and on brain stimulation did not change three and 12 months after STN-DBS surgery. In two earlier studies (Toth *et al.*, 1997; Delikanaki-Skaribas *et al.*, 2009), REE was measured during indirect calorimetry. In these studies, they found a value about 20% lower than that found in the present study. Increased rigidity, dystonia and tremor with more severe PD in our study may account for the higher REE in comparison with these other studies.

To investigate whether the medication or the brain stimulation *per se* after surgery influences the REE, we measured the REE

during different situations in the two postoperative measurements (Fig. 1). We found that the REE was not significantly different during 'off' medication and 'off' stimulation compared with the values 'on' medication and 'on' stimulation. This is in contrast to the results by others (Perlemoine *et al.*, 2005; Montaurier *et al.*, 2007), but the discrepancy is probably due to differences in the two studies as the other study investigated the patients during acute L-dopa challenge and acute brain stimulation (30 min), while in our study the 'off/off' measurements were performed after the stimulation, and anti-parkinsonian medication was removed for 12 h before the measurements. The present study also showed that the DBS *per se* significantly decreased the lipid oxidation rate during 'on' stimulation. This change in substrate oxidation rate has been observed by others (Perlemoine *et al.*, 2005). There is no obvious explanation for the shift in substrate oxidation rates. However, measurements on rats after 30 s of electrical stimulation of the hypothalamus showed increases in energy expenditure and increases in RER, suggesting that the hypothalamic activity influences which substrate the rat uses for energy and that hypothalamus forms part of body weight regulation (Atrens *et al.*, 1987).

The reported daily physical activity level and the fitness as measured by peak oxygen uptake were unchanged postoperatively. The patients improved their motor function postoperatively (UPDRS III), and in general these patients improve their physical activity so it cannot be excluded that the scale used has a too low sensitivity in this type of patients, or the number of subjects was too low. On the other hand, all the investigated patients increased their body weight postoperatively.

Under-reporting of food intake is frequent and has earlier been shown by the doubly labelled water method (Schoeller, 1990; Trabulsi & Schoeller, 2001; Ferriolli *et al.*, 2010). In an earlier review, they found about 25% under-reporting under different conditions. In our study, the under-reporting was about 25% and not significantly different in the pre- and postoperative period. The reported dietary intake was significantly decreased at 12 months postoperatively in spite of weight gain in the same period. This suggest that the positive weight balance postoperatively in the STN-DBS patients is not because of increased appetite and thereby increased energy intake as proposed in an earlier abstract by Barichella *et al.* (2002). Nevertheless, in a later article from the same group they found that the weight gain after STN-DBS operation was independent of increase in appetite and therefore an unlikely explanation (Barichella *et al.*, 2003), which has been confirmed by other prospective studies (Montaurier *et al.*, 2007; Sauleau *et al.*, 2009). However, inaccuracy of self-reported intakes should prompt caution in the interpretation of the result.

The study has shown that the DEE decreases after STN-DBS surgery, so a likely explanation of the weight gain is that brain stimulation induces an imbalance between energy intake and energy expenditure. It can be speculated whether STN DBS *per se* has a central 'weight modifying' effect, as proposed in recent studies (Strowd *et al.*, 2010; Locke *et al.*, 2011). The expected postoperative weight gain can be prevented by nutritional intervention starting up early after the operation if weight gain is not welcome (Guimaraes *et al.*, 2009).

The patients were in positive energy balance during the study, and the indirect measurements of energy expenditure assume steady state. However, the measurements of free-living energy expenditure were taken during 14 days, and in this period, the weight gain was on average 0·2 kg. This will only influence the RQ and energy equivalent of carbon dioxide with <1% (Elia, 1991).

Limitations

This study is one of the few long-term prospective studies where energy intake and energy expenditure have been extensively evaluated before and after STN-DBS. However, the number of patients is limited, so there can be risk of type 2 statistical errors.

Conclusion

The STN-DBS operated patients have a significant postoperative weight gain, and the weight gain is taking place in the fat mass. The increase in weight is attributed to a decrease in free-living energy expenditure concomitant with a simultaneous insufficient decrease in energy intake. The marked changes in free-living DEE observed after STN-DBS operation in Parkinson patients may have important implications in terms of practical and clinical recommendations for reducing energy intake if weight gain is not welcome postoperatively.

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